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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	10/066,496	EMBERLY ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-28 is/are rejected.

7)☒ Claim(s) 1 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-28 are examined on the merits.

SEQUENCE COMPLIANCE

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). See, for example, table on page 25. However, this application fails to comply with the requirements of 37 CFR § 1.821 through 1.825 because said table on page 25, contain amino acid sequences with sequence lengths that are equal to or greater than 4 amino acid molecules and these sequences do not have SEQ ID Nos cited along with each sequence in the specification. Applicants are also reminded that a CD-ROM sequence listing submission may replace the paper and computer readable form sequence listing copies. Applicant(s) are required to submit a new computer readable form sequence listing, a paper copy for the specification, statements under 37 CFR § 1.821(f) and (g), if there is a need to list additional sequences in the listing. Applicant(s) are given the same response time regarding this failure to comply as that set forth to respond to this office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

OBJECTIONS

3. Claim 1 is objected to because of the following informalities: Claim 1 contains improper periods in "a.", "b.", and "c.", for example. Appropriate correction is required.

CLAIM REJECTIONS - 35 U.S.C. § 112, SECOND PARAGRAPH

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Specific to claim 1, the limitation of "protein backbone configuration" is recited in the preamble, while the body of said claim lacks any recitation of "protein", "backbone", or "configurations" limitation. Does the preamble or the actual steps of the claim control the metes and bounds of claim 1. Clarification of the metes and bounds is required. Claims 2-28 are rejected for being dependent from claim 1.

7. Specific to claims 9, 13, and 15, line 1; and claim 20, line 2, said claims recite the phrase "wherein step (b)" causes said claims to be vague and indefinite because said step "(b)" does not exist in the dependent from claim 1. Clarification of the metes and bounds is required. Claims 10-12, 14, 16-19, 21, 22, and 25 are rejected for being dependent from claim 9, 13, 15, or 20, respectively.

8. Specific to claims 13, lines 2-3, and 14, lines 1-2, the recitation of "a predetermined constraint" causes the claims to be vague and indefinite because said constraint has never been determined in dependent from claim 1. Therefore, the instant claims are unclear as to whether the constraint is "predetermined" in the dependent from claim 1 or some other step that has not been specified in the instant claims. Clarification of the metes and bounds is required.

9. Specific to claim 22, the Applicant uses the abbreviations of "crms". Abbreviations in claims are vague and indefinite unless accompanied by the full name, usually in parentheses.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 26-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

12. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

13. Specific to the equation for determining $E_{designability}$ of claim 26, the term h_i has not being defined in the specification to the extend which would enable one of skill in the art to predictably

practice the claim invention as recited by claims 26-28 without any undue experimentation. It is noted the instant specification discloses that $h_i = h_o$ +/- δh and h_o is determined by fitting the surface-area distribution of a set of natural four-helix bundles to the surface-area distributions for the 100 most designable four-helix-stacks. The best fit preferably corresponds to $h_o = 2kbT$ and hydrophobic residues have a hydrophobicity of $5k_bT$ and polar residues $-1k_bT$. However, the instant specification does not provide guidance as how one of skill in the art would determine by fitting the surface-area distribution of a set of natural four-helix bundles to the surface-area distributions for the 100 most designable four-helix-stacks. What fitting criteria are being used to select the 100 most designable four-helix-stacks to calculate h_o? How does one of skill in the art arrive at the values of $h_o = 2kbT$ and hydrophobic residues have a hydrophobicity of $5k_bT$ and polar residues $-1k_bT$? Therefore, one of skill in the art would not be able to predictably practice the claimed invention as directed to determining $E_{designability}$ without knowing how h_i is derived via h_o.

CLAIM REJECTIONS - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-8, 13-15, 20, 23, and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Dahiyat et al. (1997).

16. Dahiyat et al. discloses a method for designing stable and well-folded (backbone configurations) proteins with novel sequences wherein said method comprises specifying a

protein having less than 30 residues containing sheet, helix, and turns structures (page 82, Abstract etc. and column 3, lines 32-34). The method of Dahiyat et al. is directed toward the screening of possible sequences for compatibility with the desired protein fold (designable) (page 82, column 1, lines 12-16) and select an amino acid sequence that will stabilize a target structure (designable) (page 82, column 2, lines 4-7), as in instant claim 1, step a, and claims 2-4.

17. The arrangement of these secondary structural elements is directed to the core and boundary position of the protein in regard to side chains, protein coil-coil designs, and hairpin turns (stack as defined by the instant specification) (page 83, column 1 to column 2, line 19; and Figure 4), as in instant claim 1, steps b and c.

18. An alignment of the sequences indicates only 6 of the 28 residues are identical and four of the identities are in the buried cluster (page 83, column 3, lines 7-14), as in instant claims 5-7.

19. The method of Dahiyat et al. comprises sedimentation equilibrium studies directed at randomly distributed residuals (page 87, References and Notes, No. 27 and 28), restrained energy minimized average from the NMR structure determination as directed to Ω and X_1 and X_2 angles (Euler angle), and Cα coordinates (page 86, Table 2), as in instant claim 8.

20. The packing pattern of the hydrophobic core of the NMR structure is used to determine the constraint criteria as directed to matching X_1 and X_2 angles, the agreement of the strand-to-helix turn, and the difference in the Φ and Ψ angles for sequence selection (page 86, column line 1 to column 2, line 34), as in instant claims 13 and 14.

21. The NMR data were collected NMR spectrometry wherein water suppression was accomplished either with pre-saturation during relaxation delay or pulsed filed gradients (page 87, References and Notes, No. 28), as in instant claim 15.

22. The total number of amino acid sequences that must be considered is the product of the number of possible amino acid at each residue position (page 83, column 1, lines 23-28) and the respective residues are classified by ranking (cluster) (Figure 1), as in instant claim 20.

23. The design algorithm of Dahiyat et al. designs proteins based on the following criteria distance restraint (constraint), protein-folding characteristics of a motif with a small hydrophobic ore, and the protein backbone is defined with a root-mean-square (rms) (page 85, columns 1-3, Experimental Validation §). Based on the criteria above, the design algorithm of Dahiyat et al. select for optimal sequence from nonoptimal sequences (Figure 1), as in instant claims 23 and 24.

CLAIM REJECTIONS - 35 USC § 103

24. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

25. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made.in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dahiyat et al. (1997) taken with Dahiyat et al. (US006403312B1).

27. Dahiyat et al. (1997) discloses the limitations to claims 1-8, 13-15, 20, 23 and 24 as discussed above.

28. However, Dahiyat et al. (1997) does not disclose the step of generating an initial stack by the conjugate gradient method as in claim 9.

29. Dahiyat et al. (US006403312B1) discloses a method for protein design comprising a step of using the conjugate gradient method for the computational prescreening process (column 30, Example 1), as in instant claim 9.

30. The above disclosure of Dahiyat et al. (1997) has been extended to claims 10, 16-18, 21, and 22. Further, the comparison of the FSD-1 and the design target is analyzed in stereoview using the best-fit superposition (symmetry) of the restrained energy minimized average NMR structure (Figure 6), as in instant claims 11 and 12.

31. "This hydrogen bond is present in 95 percent of the structure ensemble and has a donor-acceptor distance of 2.6 +/- 0.06 A" (about 1.5 Angstroms) (Dahiyat et al. (1997), page 86, column 1, lines 34-44), as in instant claim 19.

32. The design algorithm of Dahiyat et al. (1997) provides a means for calculating surface exposure values (Dahiyat et al. (1997), page 87, References and Notes, No. 15), as in instant claim 25.

33. Dahiyat et al. (1997) discloses an improvement for designing stable, well-folded proteins with a fully automated novel sequence selection (Abstract etc. and page 82, column 1, lines 1-3).

34. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by the improvement disclosed by Dahiyat et al. (1997) to design stable, well-folded proteins with a fully automated novel sequence selection using a protein library as taught by Dahiyat et al. (US006403312B1). Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to design stable, well-folded proteins with a fully automated novel sequence selection using a protein library as taught by Dahiyat et al. (1997) and Dahiyat et al. (US006403312B1).

CONCLUSION

35. NO CLAIM IS ALLOWED.

36. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

38. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

39. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

C. Dune Ly
3/2/04

ARDIN H. MARSCHEL
PRIMARY EXAMINER